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论著

人肝CYP3A参与了山冈囊吾碱的代谢及其肝毒性代谢物的形成

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摘要 目的 在体外研究山冈囊吾碱在人肝微粒体内的代谢及参与其代谢的主要的CYP450酶，探讨其代谢致毒机理。方法 采用人肝微粒体研究山冈囊吾碱的主要代谢方式和代谢物。在体外运用CYP450酶的选择性抑制剂和cDNA表达的人肝CYP450酶，探讨其对山冈囊吾碱的代谢及肝毒性的吡咯代谢物形成的影响及参与山冈囊吾碱代谢的主要的CYP450酶。结果 山冈囊吾碱在人肝微粒体内的主要代谢物为肝毒性的吡咯代谢物：去氢倒千里光裂碱，7-谷胱甘肽基-去氢倒千里光裂碱，7,9-二谷胱甘肽基去氢倒千里光裂碱和山冈囊吾酸。CYP450特异性抑制剂α-萘黄酮(抑制CYP1A2)、黄胺苯吡唑(抑制CYP2C)、奎尼丁(抑制CYP2D6)和二乙基二硫代氨基甲酸钠(抑制CYP2E1)对山冈囊吾碱的代谢无明显的影响。但CYP3A的特异性抑制剂酮康唑和三乙酰竹桃霉素可以显著地抑制山冈囊吾碱的代谢及其吡咯代谢物和结合型吡咯物的形成。此外，在cDNA表达的人肝CYP3A4的温孵液中，山冈囊吾碱被代谢成相应的吡咯代谢物，而山冈囊吾碱在cDNA表达的人肝CYP1A2、CYP2C9、CYP2D6和CYP2E1温孵液中无代谢。结论 山冈囊吾碱在人肝微粒体内的主要代谢方式是形成肝毒性吡咯代谢物，CYP3A作为主要的CYP450酶参与了山冈囊吾碱的代谢及其肝毒性吡咯代谢物的形成。CYP3A在山冈囊吾碱所致的肝毒性中发挥了重要的作用。

关键词 山冈囊吾碱 肝脏 微粒体 生物转化

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Involvement of human CYP3A4 in the formation of hepatotoxic metabolites of clivorine

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Abstract

AIM This study was conducted to identify the human CYP isoforms responsible for the biotransformation of clivorine in human liver microsomes and the mechanism of metabolism-induced hepatotoxicity of clivorine. **METHODS** Human liver microsomes were used to investigate the metabolism of clivorine *in vitro*. Selective CYP-450 inhibitors and cDNA expressed human CYPs were used to study their effects on the formation of hepatotoxic meta bolites and the metabolism of clivorine and the principal CYP-450 isoform involved in the formation of hepatotoxic metabolite. **RESULTS** Four metabolites, namely dehydroretronecine(DHR), 7-glutathionyl-dehydroretronecine(7-GSH-DHR), 7,9-diglutathionyl-dehydroretronecine(7,9- diGSH-DHR) and clivoric acid were found in the microsomal incubations. Chemical inhibition studies indicated that the metabolism of clivorine and the formation of pyrrolic metabolites as well as the bound pyrroles were strongly inhibited by CYP3A inhibitor ketoconazole(Ket). Whereas α-naphthoflavone (Nap), sulfaphenazole(Sulp), quinidine(Qui), diethyldithiocarbamate(DDC) have no significant effects on the metabolism of clivorine and the formation of pyrrolic metabolites in human liver microsomes. The results of metabolism of clivorine by cDNA expressed human CYPs showed that only CYP3A4 was found to be capable of catalyzing the metabolism of clivorine, while CYP1A2, CYP2C9, CYP2D6 and CYP2E1 did not play significant roles in the metabolism of clivorine and [the formation of pyrrolic metabolites. **CONCLUSION** The results demonstrated that the pyrrolic metabolites were the major *in vitro* metabolites of civorine and CYP3A4 was the major CYP isoform involved in clivorine metabolism and the formation of hepatotoxic pyrrolic metabolites in human liver microsomes. CYP3A4 plays a key role in the clivorine induced hepatotoxicity.

Key words clivorine liver microsome biotransformation

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